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In Vivo Efficacy of Trovafloxacin (CP-99,217), a New Quinolone, in Experimental Intra-Abdominal Abscesses Caused by *Bacteroides fragilis* and *Escherichia coli*

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The efficacy of trovafloxacin in treating *Bacteroides fragilis* and *Escherichia coli* infections was investigated and compared to the efficacy of combined clindamycin and gentamicin therapy in an experimental model of intra-abdominal abscesses in rats. Rats were treated with different doses of CP-116,517-27, a parenteral prodrug of trovafloxacin. Response to treatment was evaluated by mortality rate and elimination of infection (cure rate). Mortality in the control group was 85.4%, whereas in rats treated with trovafloxacin, it was close to 0%. The highest cure rate (89.3%) resulted from the administration of 40 mg of CP-116,517-27 per kg of body weight three times a day (TID) for 10 days (equivalent to 18.15 mg of active drug trovafloxacin per rat per day). The therapeutic response with trovafloxacin was comparable to that of a combination therapy of clindamycin (75 mg/kg) plus gentamicin (20 mg/kg) TID (cure rate, 74%; mortality rate, 5%). The measured peak levels of trovafloxacin in serum and abscess pus were 2.6 ± 0.3 and 5.2 μg/ml, respectively. The tumor necrosis factor alpha levels in the untreated animals were high compared to those for rats treated with trovafloxacin or clindamycin plus gentamicin. These results demonstrate that trovafloxacin as a single agent appears to be as successful as clindamycin plus gentamicin in the treatment of experimental intra-abdominal abscesses in rats.

It is now well-recognized that most intra-abdominal infections involve multiple bacteria. The most frequently encountered organisms in intra-abdominal abscesses are *Escherichia coli* and *Bacteroides fragilis* (14). These two organisms are a normal part of fecal flora but can cause intra-abdominal abscess following surgery. An effective antimicrobial for the treatment of intra-abdominal infections, therefore, requires a broad spectrum of activity against both aerobic and anaerobic bacteria.

Trovafloxacin (CP-99,219), a new fluoroquinolone with a structure differing from those of ciprofloxacin, norfloxacin, ofloxacin, and enoxacin, is shown to be highly active in vitro against both *E. coli* (range of MICs at which 90% of the isolates were inhibited [MIC_{90}], 0.06 to 0.12) and *B. fragilis* (MIC_{90} range, 0.6 to 1 μg/ml) (10, 12). Studies of the in vivo efficacy of trovafloxacin in mixed aerobic and anaerobic infections are very limited. Recently, it has been reported that trovafloxacin, unlike other quinolones, was active in reducing the numbers of *E. coli* and *B. fragilis* in a mouse model of localized subcutaneous infection (7). In this study, we compared the in vivo activity of trovafloxacin (CP-99,219) with that of a combination of clindamycin plus gentamicin in an experimental model of intra-abdominal abscess (IAA) caused by *E. coli* and *B. fragilis.*

MATERIALS AND METHODS

Animals. Male Sprague-Dawley rats weighing 150 to 200 g were purchased from Simonsen Laboratories, Gilroy, Calif. All animals were housed at the animal care facility at our institute, and they were fed ad libitum.

Antibiotics. CP-116,517-27, a parenteral prodrug, and the active drug trovafloxacin (CP-99,219-27) were kindly provided by Pfizer Pharmaceuticals, Groton, Conn., for in vivo and in vitro susceptibility testing. Clindamycin sulfate (Upjohn, Kalamazoo, Mich.) and gentamicin (Lyphomed, Deerfield, Ill.) were purchased from the Pharmacy, King/Drew Medical Center, Los Angeles, Calif.

Bacterial isolates. *E. coli* (ATCC 25922) was obtained from the American Type Culture Collection and was grown in brain heart infusion broth. *B. fragilis* used in this study was an isolate from a patient with an IAA, and it was grown in prereduced chopped meat broth.

Antimicrobial susceptibility. The in vitro susceptibilities of *E. coli* and *B. fragilis* to trovafloxacin and clindamycin plus gentamicin were determined by the broth microdilution method as previously described (1).

Experimental model. Details of the induction of IAAs in rats have been previously described (16, 17, 19). Briefly, IAAs in rats were induced by implanting a gelatin capsule filled with an abscess-forming mixture of *E. coli* (1.5×10^5/CFU) and *B. fragilis* (3×10^7/CFU) plus sterile rat feces and 10% $BaSO_4$. Before use in the rat IAA model, both organisms were passaged through the peritoneal cavities of rats.

Antibiotic therapy was initiated 4 h postinoculation. Rats were treated with CP-116,517-27, a parenteral prodrug of trovafloxacin (CP-99,219), or clindamycin plus gentamicin. A group of animals inoculated with bacteria, but left untreated, served as controls. Different therapeutic schedules and doses of CP-116,517-27 were evaluated to determine the optimal therapeutic regimen to sterilize abscess pus in experimental IAAs in rats. These were 20 mg/kg of body weight three times a day (TID) at 4-h intervals, 30 mg/kg TID, 40 mg/kg TID, 40 mg/kg twice a day (BID) at 8 h apart, 60 mg/kg once a day (QD), and 60 mg/kg BID. Preliminary studies showed that at the selected dosages, levels of trovafloxacin in the serum were higher than the MIC against the test organisms used in this study. The doses of clindamycin and gentamicin were 75 and 20 mg/kg, respectively, and the doses used were based on our previous studies (16, 17). Clindamycin plus gentamicin was administered TID at 4-h intervals. All antibiotics were administered intramuscularly for 10 days.

Assessment of results. Rats were euthanized on day 12. The abdomens of the animals were then opened and examined for abscesses. Pus was collected and cultured for 72 h for both *E. coli* and *B. fragilis. E. coli* was identified by conventional methods, and *B. fragilis* was identified by the method described in the Virginia Polytechnic Institute Anaerobic Laboratory manual. In the present study, absence of cultivable organisms in the abscess pus was considered a cure, and pus in which either of the organisms used in the inoculum grew was considered evidence of failed treatment. The therapeutic schedules that cured IAAs were repeated to verify the observations. For the sake of brevity, results obtained from separate experiments were combined.

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Measurement of levels of trovafloxacin in the serum and tissues. A separate set of rats inoculated with *E. coli* and *B. fragilis* were treated with the prodrug of trovafloxacin (40 mg/kg TID) for 10 days. On day 11, the rats were injected with trovafloxacin, and at different time intervals the rats were exsanguinated and tissue samples were collected. The samples were immediately frozen at −70°C. Levels of trovafloxacin in the serum and tissues were analyzed by high-performance liquid chromatography (HPLC) as previously described (5, 13). Briefly, 200 μl of rat serum was acidified by adding 500 μl of 0.025 M KH_2PO_4 (pH 3). An internal standard (methyl derivative of trovafloxacin) was added to the acidified serum, and the mixture was applied onto a Polysorb C-18 MP-1 solid-phase extraction column (Interaction Chromatography Inc., San Jose, Calif.). Trovafloxacin and internal standard were eluted from the column with 2 ml of HPLC-grade methanol, which was subsequently evaporated at 55°C under a stream of nitrogen. The residue was redissolved in 0.5 ml of mobile phase (0.04 M H_2PO_4-acetonitrile-tetrabutyl ammonium-hydroxide-0.0005 M dibutyl amine phosphate [D-4] reagent; 83/16.85/0.05/0.1 [vol/vol/vol/vol]; pH 3.0) and filtered, and aliquots (50 μl) were injected directly onto the HPLC column (3.9 by 150 mm; Waters Novapak C-18; Waters Chromatography, Milford, Mass.). Elution of trovafloxacin at 275 nM was monitored. Trovafloxacin concentrations in rat tissue were determined by the following procedure. Approximately 0.5 g of thawed tissue was added to 5 ml of extraction buffer (0.15 M $HClO_3$, 0.15 M H_2PO_4 in distilled H_2O-CH_3OH; 50/50 [vol/vol]). An internal standard (a methyl derivative of trovafloxacin) was then added to each sample, and the samples were homogenized. The samples were subsequently centrifuged, and the resulting supernatant was evaporated to near dryness at 55°C under a stream of nitrogen. The residue was dissolved in 2 ml of 0.025 M KH_2PO_4 (pH 3.0) and extracted twice with 5 ml of ethyl acetate. The ethyl acetate layers were combined and evaporated as previously described. The residue was resuspended in 0.5 ml of mobile phase (see above) and washed with 1 ml of hexane. The hexane layer was aspirated off, and 50-μl aliquots were injected onto the HPLC column as described above.

Measurement of TNF-α in serum. Rats were inoculated with an abscess-forming mixture of *E. coli* and *B. fragilis*, and therapy (trovafloxacin prodrug, 60 mg/kg BID) was initiated 4 h after inoculation. Serum samples were collected prior to therapy (4 h postinfection) and at 24, 48, 72, and 96 h posttherapy. Serum samples collected from infected rats not treated with antibiotic served as controls. Serum samples collected immediately after infection served as 0-h samples. Additional experiments were done to determine whether antibiotic therapy could reduce circulating tumor necrosis factor alpha (TNF-α) levels in rats injected with nonviable bacteria. In these experiments, rats were injected with heat-killed *E. coli* and *B. fragilis* and treated with trovafloxacin or with clindamycin plus gentamicin. Serum samples were collected at the time points described above. TNF-α in serum was quantified by enzyme-linked immunosorbent assaying (BioSource international, Camarillo, Calif.) according to the manufacturer's recommended procedure. Results were analyzed by the Student *t* test.

Statistics. Results (percent cured) were compared for all treatment regimens and control animals. The difference in proportions from several independent samples was compared utilizing the chi-square procedure as described by Fleiss (6). A chi-square value corresponding to a *P* value of less than 0.05 was considered statistically significant.

RESULTS

Antimicrobial susceptibility. The MICs of trovafloxacin against *B. fragilis* and *E. coli* used in this study were 0.24 and 0.03 μg/ml, respectively. *B. fragilis* was susceptible to clindamycin at 1.5 μg/ml, whereas *E. coli* was susceptible to gentamicin at 1.9 μg/ml.

Effects of different trovafloxacin therapeutic schedules on the survival of rats inoculated with *E. coli* and *B. fragilis* and on the cure of IAA. Results are shown in Table 1. In the control group, 85% of the rats inoculated with *E. coli* and *B. fragilis* died within the first 3 days. At autopsy, these animals showed no abscesses. Both *E. coli* and *B. fragilis* were recovered from the peritoneal fluid of dead animals when autopsy was done soon after death (six of six animals). However, a delayed autopsy resulted in recovery of *E. coli* but not *B. fragilis*, possibly due to an overgrowth of *E. coli*. Six animals (15%) lived 2 weeks after inoculation of bacteria, and, at autopsy, all animals had IAAs and *E. coli* and *B. fragilis* were recovered from the abscess pus.

Regardless of the dose used for the treatment, trovafloxacin protected the rats from death due to acute bacterial infection (Table 1). The survival rate of rats treated with a single drug, trovafloxacin (93 to 100%), was essentially similar to that of rats treated with a drug combination of clindamycin and gentamicin (94%).

TABLE 1. Effect of different therapeutic schedules on sterilization of pus in experimental IAA due to *B. fragilis* and *E. coli*

Dose of prodrug CP-116,517-27 (mg/kg)[a]	Days of reaction	No. of rats alive/ no. of rats per group (% mortality)	Pus culture + VE		
			E. coli	*B. fragilis*	% Cure
Controls	10	6/41 (85.4)[b]	6	6	0
20 TID	10	12/12 (0)	7	6	42
30 TID	10	14/14 (0)	10	6	29[d]
40 TID	10	27/28 (3.5)[c]	3	3	89[e]
40 BID	10	15/15 (0)	8	3	47
60 BID	10	11/11 (0)	6	3	46
60 QD	10	14/15 (6.7)	7	5	53
60 QD	15	12/12 (0)	5	5	58
75 clindamycin + 40 gentamicin TID	10	36/38 (5.3)[b]	10	4	74[e]

[a] 1-mg amount of prodrug CP-116,517-27 is equal to 0.605 mg (60.5%) of the active drug trovafloxacin (CP-99,219).
[b] Results of three separate experiments.
[c] Results of two separate experiments.
[d] $P \leq 0.005$ compared with all other dosages and regimens.
[e] $P \leq 0.01$ compared with groups of rats treated (in milligrams per kilogram) with 20 and 30 TID, 40 BID, 60 QD, and 60 BID.

The cure rate for trovafloxacin-treated animals was dependent on the therapeutic schedule; it varied from 29 to 89%. The cure rate in rats treated with a combination of clindamycin and gentamicin was 74%, whereas in control rats it was 0%. There was a statistically significant difference in the proportion of animals cured ($\chi^2 = 32.10$; $P = <0.001$; 9 df). Subsequent analysis of the contribution of each regimen to the difference observed revealed that 40 mg/kg TID and clindamycin plus gentamicin showed significantly greater efficacy than all of other dosage and regimens ($\chi^2 = 19.3$; $P < 0.01$; 4 df). The cure rate with a single drug, trovafloxacin, given at 40 mg/kg TID was not significantly different from that of rats treated with clindamycin (75 mg/kg) and gentamicin (20 mg/kg) TID ($P \geq 0.05$). Oddly, the 30-mg/kg TID regimen showed significantly lower efficacy than all of the other regimens. This difference was statistically different at the $P < 0.005$ level.

In animals that failed with trovafloxacin prodrug therapeutic schedules or with clindamycin and gentamicin combination therapy, both *E. coli* and *B. fragilis* were recovered from the IAA pus. Considering that 1 mg of prodrug was equivalent to 0.605 mg of active trovafloxacin, the most effective dosage of trovafloxacin was 18.12 mg per rat per day.

Trovafloxacin concentration in serum and tissues. The measured peak levels of trovafloxacin in the serum and abscess pus of rats treated with 40 mg of prodrug per kg TID were 2.6 ± 0.3 and 5.2 μg/ml, respectively (Table 2). Trovafloxacin levels in other tissues were in general two to four times higher than that found in serum. We reported earlier that the peak levels of gentamicin and clindamycin in the serum of rats were 3 to 5.1 and 6.8 μg/ml, respectively (16, 17).

Levels of TNF-α in serum of rats treated with antibiotics. TNF-α has been shown to produce death and shock similar to what is seen after gram-negative infections (3, 4, 8, 18). Experiments were performed to determine whether increased survival levels of rats treated with trovafloxacin or clindamycin plus gentamicin were associated with decreased levels of TNF-α circulating in serum. In control animals, the TNF-α levels peaked 24 h after inoculation of bacteria (Fig. 1A and B). All control animals died within 3 days. In animals treated with trovafloxacin or clindamycin plus gentamicin, the peak

TABLE 2. Concentrations of trovafloxacin in serum and tissues after intramuscular injection of 40 mg of prodrug (CP-116,517-27) per kg in rats

Sample	Concn at the following h postinjection[a]			
	1	T/S	4	T/S
Serum	2.7 ± 0.3	1.0	0.5 ± 0.4	1.0
Abscess	5.2	1.9	2.3 ± 1.3	4.6
Spleen	6.5 ± 3.1	2.4	0.7 ± 0.4	1.4
Liver	3.8 ± 1.4	1.4	0.8 ± 0.4	1.6
Lung	3.4 ± 1.1	1.3	0.7 ± 0.4	1.4
Intestine	6.1 ± 1.1	2.3	0.8 ± 0.4	1.6

[a] Antibiotic concentrations were determined by HPLC. Concentrations of drug in serum and tissues are in micrograms per milliliter and micrograms per gram, respectively. T/S, tissue-to-serum ratio.

levels of TNF-α in serum were significantly lower than those for uninfected controls, and none of the treated animals died. Table 3 shows levels of circulating TNF-α in rats injected with heat-killed *E. coli* and *B. fragilis* and treated with trovafloxacin or clindamycin plus gentamicin. The data show that the average levels of TNF-α in rats treated with trovafloxacin but not with clindamycin plus gentamicin were lower than those for untreated control rats.

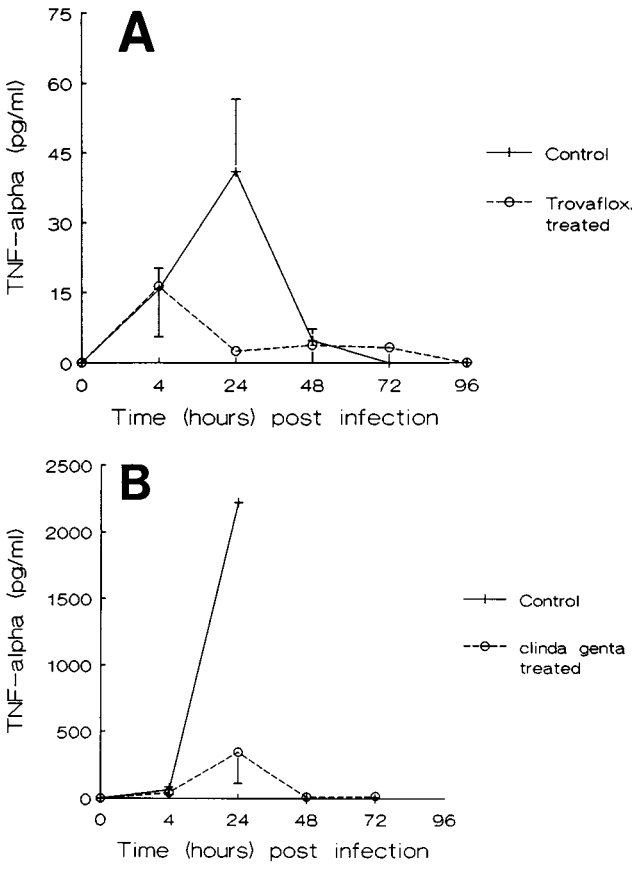

FIG. 1. Levels of TNF-α in serum of rats treated with trovafloxacin (trovaflox) (A) and clindamycin (clinda) plus gentamicin (genta) (B). Rats were infected with *E. coli* and *B. fragilis* and were treated with trovafloxacin, with clindamycin plus gentamicin, or with saline (control) as described in Materials and Methods. Serum samples were collected at the indicated time intervals, and levels of TNF-α in serum samples were measured by enzyme-linked immunosorbent assay.

TABLE 3. In vivo effects of trovafloxacin and of clindamycin plus gentamicin on TNF-α production induced by heat-killed *E. coli* and *B. fragilis*

Time (h) posttreatment	TNF-α (pg/ml) in rats treated with		
	Saline	Trovafloxacin	Clindamycin + Gentamicin
0	<15	<15	<15
4	208 ± 36	65.6 ± 57[a]	179 ± 33
24	38 ± 19	<15	29 ± 69
48	<15	<15	<15

[a] $P = <0.05$.

DISCUSSION

Our results show that trovafloxacin protected rats against death due to sepsis caused by *E. coli* and *B. fragilis*. The data further indicate that the most effective regimen in clearing mixed *B. fragilis* and *E. coli* infections was 40 mg of trovafloxacin prodrug per kg. This activity of trovafloxacin against experimental infection is comparable to the in vivo activity of the clindamycin-plus-gentamicin combination. Girard et al. (7) reported that when trovafloxacin was given at 100 mg/kg, it was effective in reducing the numbers of recoverable *E. coli* and *B. fragilis* in a mouse model of subcutaneous abscess. Taken together, these data suggest that trovafloxacin is a worthy candidate for clinical evaluation in *B. fragilis*-associated infections.

In this study, we did not compare the activity of trovafloxacin with those of other quinolone antibiotics. However, using a rat model of IAA, we have previously reported that ciprofloxacin, temafloxacin, difloxacin, and A56620 eliminated *B. fragilis* infections in 90 to 95% of the animals when given at 40 mg/kg TID for 10 days. At this dosage, the achieved levels of ciprofloxacin, temafloxacin, difloxacin, and A56620 in serum were 1.7, 8, 14.3, and 1.9 μg/ml, respectively (15–17). Previous studies also have indicated that quinolones reach higher concentrations in tissue and pus than in the serum. The present study confirms these reports for the new drug trovafloxacin. The high tissue concentrations may be one of the important factors for the efficacy of trovafloxacin and possibly other quinolones in the rat model of IAA. The effective dose of the prodrug of trovafloxacin used in this study was the same as those of ciprofloxacin, temafloxacin, and difloxacin on the weight basis (40 mg/kg). It must be noted here that 40 mg of prodrug CP-116,517-27 is equivalent to 24.2 mg of active drug trovafloxacin. Therefore, the active drug concentration should be taken into consideration when comparing the in vivo activities of various quinolones.

The mechanisms by which trovafloxacin therapy protected the rats against death is not known. Trovafloxacin at dosages and regimens that failed to eliminate infection was found to protect the animals against death (Table 1). This lack of correlation between survival and elimination of bacteria suggests that factors in addition to reduction in bacterial load may also play a role in the protection of infected rats treated with antibiotics. Several studies have shown that increased levels of cytokine TNF-α are frequently associated with lethal infection and that agents that are known to decrease TNF-α levels dramatically reduce mortality (3, 4, 8, 9, 18). Our observation that increased survival of rats treated with trovafloxacin or clindamycin plus gentamicin was associated with decreased levels of TNF-α circulating in serum is consistent with the above reports. We have previously shown that rufloxacin and ciprofloxacin diminish the levels of TNF-α in serum in mice infected with *B. fragilis* (8). Yasumoto et al. (20) reported that sparofloxacin therapy resulted in decreased levels of TNF-α in sem-

inal plasma of patients with nonbacterial prostatitis. Nemunaitis et al. (11) reported that ciprofloxacin and pentoxifylline reduced levels of circulating TNF-α in serum in patients with myelodysplastic syndrome. Bailey et al. (2) showed that quinolone antibiotics inhibit production of TNF-α by monocytes activated with bacterial lipopolysaccharide. In the present study, we showed that trovafloxacin partially reduced levels of TNF-α circulating in serum in rats injected with heat-killed bacteria (Table 3). Taken together, these data suggest that trovafloxacin, like other quinolones, reduces levels of circulating TNF-α in part by modulating the production and/or secretion of TNF-α by host cells and in part by eliminating bacteria that stimulate the production of the inflammatory cytokine. The observation that clindamycin and gentamicin failed to decrease levels of TNF-α in serum in rats injected with heat-killed bacteria supports the concept that different antibiotics bring about suppression of cytokine production by different mechanisms.

In summary, trovafloxacin, a new trifluoroquinole active in vitro against *B. fragilis*, is also effective in the treatment of *B. fragilis*-associated experimental IAAs in rats.

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